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Review Article

Down Syndrome and Periodontal Disease: Role of the Immune System

Beatriz de Brito Bezerra*, DDS, MS, PhD, Sangeeta Gajendra, DDS, MPH, MS

Eastman Institute for Oral Health, University of Rochester, USA

**Corresponding author: Dr. Beatriz de Brito Bezerra, 625 Elmwood Ave, Rochester, NY 14620, United States, Tel: (585) 275-1147; Email: Beatriz_debritobezerra@urmc.rochester.edu*

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Abstract

Periodontal disease is highly prevalent in Down syndrome (DS) individuals and is a significant cause of tooth loss in these individuals. Alterations in the immune system associated with poor oral hygiene, normally observed in these patients, are important contributing factors for the increased susceptibility to periodontal disease. The etiology of periodontal disease in DS is complex and more recently much focus has been placed in understanding the immune response alterations resulting from this genetic disorder. The purpose of this paper is to review the literature on the immunological alterations observed in Down syndrome patients and their relationship to periodontal disease. The increased incidence of periodontal disease in DS subjects relates to its genetic background. The reduced ability of the immune system to properly eliminate periodontal pathogens may be the main reason behind the increased susceptibility to periodontitis. Evaluation, treatment and monitoring of these patients as early as during the primary dentition can reduce the morbidity associated with periodontal disease.

Keywords: Periodontal disease; Down syndrome; Immunology

Introduction

Down syndrome (DS), or trisomy 21, is a chromosomal disorder that affects an estimated one in 691 live births in the United States each year [1]. In developed nations, life expectancy of individuals with DS has improved with average life expectancy reaching 50 to 60 years [2]. It is a very frequent autosomal chromosomal disorder caused by an error in cell division that results in the presence of all or part of an extra chromosome 21. The over expression of specific genes found on chromosome 21 causes a complex condition with more than 80 clinical features including midfacial hypoplasia, delayed tooth eruption and high incidence of periodontal disease [3].

First described by J.L.H. Down, in 1866, as a chromosomal malformation syndrome, it is nowadays, the most prevalent of this type of malformations. The chromosomal anomaly was first observed by Lejeune, in 1959, by karyotyping, and consists of an extra copy of the chromosome 21. The specific factors responsible for this chromosomal alteration are still debatable. However, factors such as advanced maternal age, familial tendency, nondisjunction of chromosome and repetitive exposure to the same environmental agent have been considered possible etiological agents [4]. Down syndrome can present as a complete trisomy of chromosome 21, it can also be due to translocation (4%), or be related to a mosaic trisomy (1%) [1]. These individuals have impaired motor skills, intellectual disability, behavioral problems and also present several medical conditions such as cardiovascular,

immunological, hematological, respiratory, neurological, and musculoskeletal abnormalities [5]. A higher prevalence of dysfunction within certain organs, such as the esophagus and thyroid gland is also observed in this syndrome [5].

Among the medical conditions observed in this syndrome some may predispose DS individuals to oral alterations. For instance, gastric dysfunctions may promote tooth wear, mainly dental erosion, diabetes can present with xerostomia, candida infections, periodontitis and delayed healing [6,7]. Alterations in the immune response make these individuals more prone to infections, i.e. periodontal disease [8].

Periodontal diseases, characterized by the destruction of the periodontium and tooth loss [9], are caused by local etiologic factors, especially dental biofilm. However, systemic disorders may reduce or alter the resistance or host response to this factor [9]. Several studies have reported that DS individuals have an increased prevalence of periodontal disease (PD) (~96%) compared to otherwise chromosomally normal, age-matched controls and other mentally handicapped patients of similar age distribution [8-10]. Therefore, the high susceptibility to PD is not only related to poor oral hygiene, but also associated with the congenital disorder. Abnormalities in the immune response are important contributing factors to the high incidence of PD in individuals with DS. Production of oxidative radicals [11,12], decreased chemotaxis and phagocytosis of polymorphonuclear leukocytes (PMNs)[12] have been associated with the syndrome. This impaired host response characterized by disturbances of the T and B lymphocyte subsets, leads to dysregulation of cytokines, chemokines and prostaglandins [13]. Limited studies are available in the literature evaluating the mechanism associated with increased prevalence of periodontal disease in Down syndrome. The purpose of this paper is to review the literature on the immunological alterations observed in individuals with Down syndrome and their relationship to periodontal disease.

Periodontal disease in Down syndrome patients

Periodontal disease is a serious and morbid oral condition among individuals with DS. Gingivitis and periodontitis begin early and their severity increases with age [14]. It is a significant cause of tooth loss among individuals with DS [15]. In addition to mental disability, altered immune/inflammatory responses in patients with DS are important contributing factors to their increased susceptibility to periodontitis [9,10,16].

The prevalence of periodontal disease among Down syndrome patients younger than 30 years old is 60 to 90%, and is characterized by greater severity than in individuals without the syndrome [9,17,18]. Severity increases with age and manifestations such as necrotizing ulcerative gingivitis (NUG) are very common [14,19]. Other findings are marginal gingivitis, gingival recessions, alveolar bone loss, furcation involvements, increased tooth mobility and tooth loss in the lower anterior region, which characterize the aggressive type of periodontal disease [3,19].

López-Pérez, et al. [9], examined 32 DS individuals and age-matched controls and found a greater extent of gingivitis and periodontitis in DS group. When comparing with subjects affected by other learning disabilities of similar age distribution, DS individuals exhibited early, rapid and generalized periodontal destruction [21,22]. In Finland, Saxen, et al. [21] compared panoramic radiographs of DS individuals with age-matched controls and reported that 84% of DS adults showed advanced bone loss of 2.5mm or more as compared with only 27% of controls. Barnett, et al. [22] examined 30 DS individuals and 30 individuals with similar mental status and reported that bone loss was found in 60% of sites of DS individuals versus 9.3% of sites in controls. Sakellari, et al. [8] investigated the severity of periodontal disease in DS individuals and compared the group with healthy individuals or cerebral palsy patients, DS individuals presented significantly higher periodontal inflammation and treatment needs than the other groups. Shaw and Saxby [20] showed that DS individuals had an alveolar bone loss pattern similar to that in juvenile periodontitis. Lower incisors were reported exhibiting early signs of alveolar bone loss in approximately 35% of DS adolescents [23]. Only one longitudinal study has investigated the development of periodontal disease in DS adults [19]. After a 7-year observation period, Agholme, et al. [19] observed that the prevalence of bone loss increased from 35% to 74% in DS individuals. This study, however, had a small sample size comprising of 33 subjects only. A key point to note was that the severity and progression of the disease was not as rapid as reported in the literature.

Many factors may be involved in the increased susceptibility to periodontal disease associated with DS [10]. Factors previously investigated included mental disability [18-24], subgingival plaque composition [24] and immune response among others [10].

Microbiology of Periodontal diseases in Down syndrome

Microbiological studies showed that individuals with DS have significantly higher levels of periodontal pathogens, including *Porphyromonas gingivalis* and *Tannerella forsythensis* [8,24,25]. However some of these studies have shown conflicting results. Meskin, et al. [26] found no differences in the prevalence of *Bacteroides melaninogenicus,* known today as *Prevotella intermedia*, in subgingival plaque from institutionalized children with DS versus normal or cerebral palsy-affected children. Cichon et al. [3] also observed increased prevalence of *P. intermedia* in subgingival plaque samples of DS subjects. Amano, et al. [15] demonstrated, by polymerase chain reaction (PCR), that 10 periodontal pathogens showed

Table 1. Prevalence of periodontopathogenic bacteria in subgingival plaque of Down syndrome and control subjects.

		Down Syndrome		Control	
Author	Bacteria	Healthy	Disease	Healthy	Disease
Cichon et al., 1998* [3]	*P. gingivalis*		16.8		11.9
	P. intermedia		26.7		13.3
	F. nucleatum		17		23.5
Amano et al., 2001** [15]	*P. gingivalis*		76.9		80
	A.actinomycetemcomitans		82.1		80
	T. denticola		53.8		70
	T. forsythia		89.7		70
	C. rectus		92.3		90
Martinez-Martinez et al., 2013§ [25]	*P. gingivalis*	26.6	53.3¶¶		
	T. forsythia	63.3	95.5¶¶		
	T. denticola	50	88.8¶¶		
Reuland-Bosma et al., 2001§§ [27]	*P. gingivalis*		47		41
	A.actinomycetemcomitans		53		35
	T. forsythia		59		65
	C. rectus		12		24
	F. nucleatum		65		88
	P. intermedia		65		53
	P. micros		53		65
Tanaka et al., 2015¶ [28]	*P. gingivalis*	5.4¶¶	29.1	1.3	18.5
	T. forsythia	7.6	235.4	4.7	55.9
	T. denticola	16.9	1,358.2¶¶	7.3	208.7

*Mean percentage levels of subgingival DNA-positive pathogens; **Frequency of occurrence (%) by PCR method; §Mean percentage levels of bacterial DNA; §§Percentage of subjects positive for each bacterium; ¶Counts of 16S rRNA of gene copies of bacteria; ¶¶ significant findings between DS and control subgroups.

an increased PCR-positive prevalence in children with DS; and Sakellari, et al.[8] found several periodontal pathogens to colonize children, adolescents and young adults with DS at higher levels than healthy individuals and patients with cerebral palsy. Reuland-Bosma et al. [27] and Khocht, et al. [24], studied the subgingival microbial composition, and found no statistical differences between subgingival samples from DS subjects and those without DS. However, a comparison of attachment loss and number of sites with probing depth ≥5mm revealed significant differences between the investigated groups, suggesting the role of the immune system in the severity of periodontal disease in DS subjects. Martinez-Martinez et al. showed a significant increase in frequency of *T. forsythia, Treponema denticola* and *P. gingivalis* in DS patients with periodontal disease compared to DS patients without periodontitis [25]. In this study *T. forsythia* was shown to be the most frequent bacterial species detected in DS subjects with and without periodontitis. And more recently Tanaka et al., [28] compared the levels of these same pathogens between DS and chromosomally normal patients at baseline and found similar levels of *P. gingivalis* and *T. forsythia* at diseased sites in both groups, however, *T. denticola* were significantly higher in DS subjects. In healthy sites of DS subjects, levels of *P. gingivalis* were greater than in normal subjects. These studies suggest that periodontopathogenic bacteria are associated with periodontal disease in DS, and their increased prevalence compared to normal subjects could be a result of the impaired immune response observed in DS. Table 1 elucidates the differences in the levels of periodontopathogenic bacteria in subgingival plaque between DS and control patients in relevant studies.

Immune response in Down syndrome

The altered host immune response observed in DS individuals is particularly important in the pathogenesis of periodontal disease. Presence of immune deficiencies, altered cell functions and alterations in oxidative stress support the findings of greater severity of PD in DS patients in several studies [11,29]. Neutrophil chemotaxis is impaired and alveolar bone loss has been shown to be inversely proportional to the chemotactic index [11]. Other immune defects associated with periodontitis in DS include lymphocyte dysfunction and altered antibody production. Inflammatory mediators and degrading enzymes were also increased in gingival crevicular fluid (GCF) of patients with DS [13,29,30].

Even though the number of neutrophils and monocytes is normal, chemotaxis and phagocytosis are reduced. Associated with the reduced number of T lymphocytes, these characteristics may contribute to the progression of PD in DS subjects [28]. In a recent study by Khocht, et al.[31], the authors investigated the phagocytic function of granulocytes and monocytes and observed that monocyte phagocytic intensity was significantly associated with attachment loss in DS subjects. Monocytes, when localized in the tissues, produce inflammatory cytokines and tissue degrading enzymes. Thus, their increased activity results in greater damage to the periodontium, which would explain the stronger relationship with periodontal damage compared to granulocyte phagocytic intensity found in the study.

Another peculiar characteristic is the overexpression of the superoxide dismutase-1 enzyme (SOD-1) encoded by the SOD-1 gene, which is located on chromosome 21. This enzyme is very important for the conversion of oxygen-derived superoxide (O_2^-) to hydrogen peroxide (H_2O_2) and its activity is increased in several tissues in Down syndrome [15]. The increased activity of SOD-1 reduces immunity in Down syndrome by damaging immune cells and impairing cellular signal transduction events during phagocytosis by increased levels of H_2O_2. With the decrease in the concentration of O_2^-, a decrease in bactericidal activity of phagocytes is observed [15].

Periodontal pathogens, such as *P. gingivalis*, stimulate periodontal cells to produce inflammatory mediators such as prostaglandin E_2 (PGE_2), matrix metalloproteinases (MMPs), and proinflammatory cytokines [32, 33]. In healthy adults increased levels of PGE_2 in the gingival crevicular fluid have been associated with the progression of periodontal disease [32, 33]. Gingival fibroblasts in DS patients, when stimulated with *A. actinomycetemcomitans* LPS, express more cyclooxygenase 2 (COX-2), which in turn induce the production of PGE_2, increasing its concentration in the GCF [34]. PGE_2 is a potent signal for bone resorption, and has been found at increased levels in the GCF of DS patient, which suggests that it can be an important factor in the pathogenesis of periodontal disease in this syndrome [30,35].

Matrix metalloproteinases (MMPs) are enzymes capable of degrading all kinds of extracellular matrix proteins. These enzymes are expressed by monocytes, macrophages, lymphocytes and polymorphonuclear cells, as well as by fibroblasts, epithelial and endothelial cells. When excessively expressed in the periodontium they promote periodontal breakdown. An increase in the activity of collagenases (MMPs 2, 8, 9) in saliva and GCF has been observed in Down syndrome children compared to healthy subjects [32]. Halinen, et al. [36] identified higher concentrations of MMP-8 in GCF of Down patients, and Komatsu, et al. [29] observed enhancement in the activity of MMP-2 in the gingival tissues and culture fibroblasts of DS patients. Komatsu, et al. [29] also observed that the inhibitory capacity of tissue inhibitor metalloproteinase 2 (TIMP-2) against MMP-2 was repressed in DS patients. In a recent study, Yamazaki-Kubota, et al. [37] investigated the levels of MMPs-2 and 8 in the GCF of DS patients without periodontitis. They observed increased levels of both MMPs in these patients compared to healthy subjects, which suggests that increased levels of these enzymes are involved in higher susceptibility to and prevalence of periodontitis in DS patients. More re-

cently Tsilingaridis, et al.[13] observed that DS patients with gingivitis compared to healthy controls with gingivitis, but not periodontitis, exhibited higher concentrations of MMPs in the GCF. In this study the relationship between MMP-8 and TIMP-2 was altered, where MMP-8 increased four-fold compared to only a two-fold increase in TIMP-2, which may result in enhanced tissue breakdown during the early stages of gingival inflammation [13]. Figure 1 shows a plausible mechanism for the association of immune system dysfunction and periodontal disease in Down syndrome.

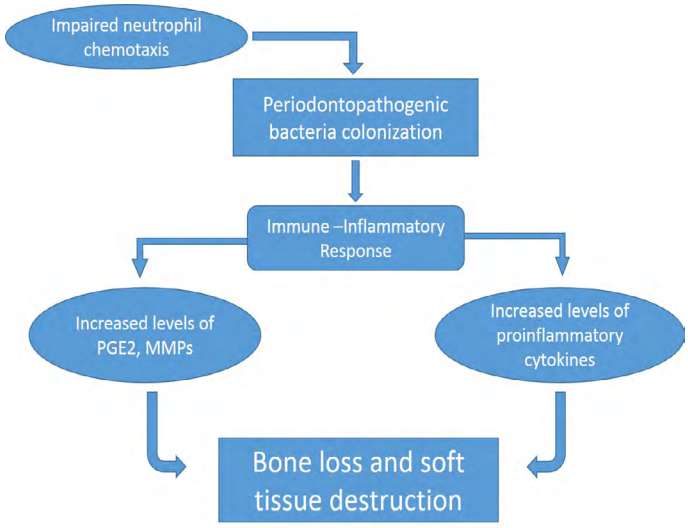

Figure 1. Plausible mechanism for the association of immune system and periodontal disease in Down syndrome.

Prevention and treatment of periodontal disease in Down syndrome patients

According to the 1999 American Academy of Periodontology classification of periodontal diseases, individuals with Down syndrome present periodontitis as a manifestation of the genetic condition [38].

As previously discussed in this paper, periodontal disease in DS individuals is not only associated with plaque accumulation but is also determined by the response of the immune system to the bacterial plaque. It is extremely important to involve the care-taker on the oral hygiene habits and preventive care to prevent the onset and progression of the disease [39, 40].

Previous studies have shown that preventive care is effective in reducing the severity and progression of periodontal disease in DS patients [39, 40]. In a longitudinal study with five DS patients, Sakellari, et al. [39] placed the patients in a frequent recall schedule, every six months, after scaling and root planing (SRP) and observed that frequent professional supragingival plaque control was effective in improving periodontal health. In this study supragingival plaque control altered the subgingival plaque composition, which suggests a role of supragingival plaque as reservoir for reinfection of treated sites. Yoshihara, et al. [40], in a cross-sectional study, compared DS subjects who frequently visited the dental clinic to those who had not been seen for over one year. Subjects who did not follow up showed increased probing depths and alveolar bone loss which suggests the beneficial effect of a periodic preventive care on the progression of periodontal disease in DS subjects.

Scaling and root planing associated with plaque control measures are still the gold standard treatment for periodontal disease [41]. Limited studies are available evaluating periodontal treatment outcomes in subjects with Down syndrome. In a split-mouth design, Zaldivar-Chiapa, et al. [11] evaluated the effectiveness of non-surgical and surgical periodontal therapies in 14 DS patients. During the one year observation period, patients were placed in a maintenance recall that included polishing and oral hygiene instructions. After one year, significant improvement in all clinical parameters was observed in both therapies compared to baseline. Surgical therapy showed better results for sites with probing depths greater than 3mm, but results were not statistically significant. These results suggest that, independent of periodontal treatment modality; professional maintenance and obligatory oral hygiene are required to control periodontal disease in DS patients.

Cheng, Leung and Corbet [42] published a prospective case series with 21 DS subjects followed up for 12 months. Subjects received SRP and adjunct use of 1% chlorhexidine gel for brushing and 0.2% chlorhexidine mouthwash. Subject recall was done every month and included SRP, prophylaxis for stain removal and oral hygiene reinforcement. At the end of the 12-month observation period all clinical parameters showed a marked decrease suggesting a satisfactory healing response after non-surgical mechanical periodontal therapy. The authors suggested that adjunct use of chlorhexidine and monthly recalls can be appropriate and beneficial for DS patients.

In a pilot study, Tanaka et al. [28] investigated the effect of SRP on clinical and microbiological parameters in DS compared to healthy subjects showed significant improvements in clinical parameters for both DS and healthy subjects. Non-surgical periodontal treatment associated with supragingival plaque control twice a month for 45 days resulted in significant improvement in probing depth, attachment level and bleeding on probing at diseased sites in both groups. These results suggest that non-surgical periodontal treatment is also effective in the treatment of periodontal disease in DS patients. This study however, showed that SRP did not reduce the bacterial counts of the investigated periodontal pathogens in diseased sites of DS subjects. This suggests other therapeutic strategies, such as antimicrobial agents and more frequent maintenance visits, may be necessary in these patients.

The use of local antimicrobial agents as an adjunct in the treatment of periodontal disease in a DS subject was presented in a case report [43]. A DS patient diagnosed with aggressive periodontitis was treated with SRP and a sustained local drug delivery system containing tetracycline hydrochloride. At re-evaluation a marked reduction in mean probing depth (from 6.3mm to 3.6mm) and gain in clinical attachment (1.3mm) were noted. Even though these results are only from a single case it suggests further investigation. Another case report showed the benefits of adjunct antimicrobial therapy in the management of periodontal disease [44]. In this report microbial culture and sensitivity test were used to guide treatment decisions. Systemic antibiotics (amoxicillin and azithromycin) were used in association with topical application of Betadine (iodine-based disinfectant) and resulted in a good outcome as reported by the authors.

Oral health care guidelines have not been well defined for DS patients and should be considered a very important part of the health care guidelines already in place for children with DS [45]. Until oral health guidelines are formulated, parents should follow the current recommendations from the American Academy of Pediatric Dentists [46] and seek dental care at the time of eruption of the first tooth and no later than 12 months of age and follow up visits according to the child's caries and periodontal risk.

Conclusion

It is imperative to understand the complex etiology of periodontal disease in Down syndrome, which involves several alterations in the immune system, to appropriately treat this disease in these individuals. The increased incidence of periodontal disease in DS subjects relates to its genetic background. The reduced ability of the immune system to properly eliminate periodontal pathogens may be the main reason behind the increased susceptibility to periodontitis. Periodontal disease is a debilitating condition frequently afflicting DS individuals and should be closely monitored by the oral health professional in an effort to prevent progression of the disease. The evaluation, treatment and monitoring of these patients as early as during the primary dentition can prevent the morbidity observed in these subjects associated with periodontal disease. Involvement of care givers on preventive care will result in lower morbidity and tooth mortality.

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